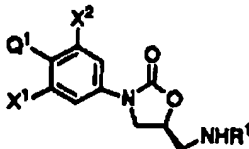


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 263/20, A61K 31/42, C07D 417/10, 455/08, 491/08, 413/10, 471/04, 491/10		A1	(11) International Publication Number: WO 97/10223
			(43) International Publication Date: 20 March 1997 (20.03.97)
(21) International Application Number: PCT/US96/14135 (22) International Filing Date: 9 September 1996 (09.09.96) (30) Priority Data: 60/003,838 15 September 1995 (15.09.95) US (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GADWOOD, Robert, C. [US/US]; 5232 Stonhenge, Kalamazoo, MI 49008 (US). KAMDAR, Bharat, V. [US/US]; 6639 Evergreen, Portage, MI 49002 (US). (74) Agent: GAMMILL, Martha, A.; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: AMINOARYL OXAZOLIDINONE N-OXIDES			
(57) Abstract			
<p>The present invention provides for aminoaryl oxazolidinone N-oxide compounds of formula (I), wherein the variables are as defined herein. These compounds are exceedingly water soluble which is useful in preparing pharmaceutical formulations of these compounds. They are also rapidly converted back to the parent amines <i>in vivo</i>, making them useful as prodrugs of the parent amines. They are effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms, such as <i>Bacteroides spp.</i> and <i>Clostridia spp.</i> species, and acid-fast organisms such as <i>Mycobacterium tuberculosis</i>, <i>Mycobacterium avium</i> and <i>Mycobacterium spp.</i>, and in organisms such as <i>Mycoplasma spp.</i></p>		 <p style="text-align: right;">(I)</p>	

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

AMINOARYL OXAZOLIDINONE N-OXIDES

FIELD OF THE INVENTION

The present invention provides for aminoaryl oxazolidinone N-oxide
5 compounds. These compounds are exceedingly water soluble which is useful in
preparing pharmaceutical formulations of these compounds. They are also rapidly
converted back to the parent amines *in vivo*, making them useful as prodrugs of the
parent amines.

These compounds have antibiotic activity comparable to the parent amines.
10 They are effective against a number of human and veterinary pathogens, including
gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci
and enterococci as well as anaerobic organisms, such as *Bacteroides spp.* and
Clostridia spp. species, and acid-fast organisms such as *Mycobacterium tuberculosis*,
Mycobacterium avium and *Mycobacterium spp.*, and in organisms such as
15 *Mycoplasma spp.*

BACKGROUND OF THE INVENTION

A variety of antibiotic oxazolidinone compounds are known in the art. For
example, please see the following:

WO 95/07271, published 16 March 1995, "Substituted Oxazine and Thiazine
20 Oxazolidinones Antimicrobials"; WO96/15130, published 23 May 1996, "Bicyclic
Oxazine and Thiazine Oxazolidinone Antibacterials"; WO96/13502, published 9 May
1996, "Phenyloxazolidinone Antimicrobials"; WO 93/23384, published 25 November
1993, "Oxazolidinone Antimicrobials Containing Substituted Diazine Moieties"; WO
90/02744, published 22 March 1990; U.S. Patent No. 5,164,510; U.S. Patent No.
25 5,225,565; U.S. Patent No. 5,182,403; "5'-Indoliny-5 β -Amidomethyloxazolidin-2-
ones"; WO 95/25106, published 21 September 1995, "Oxazolidinone Derivatives and
Pharmaceutical Compositions Containing Them"; WO 93/09103, published 13 May
1993, "Substituted Aryl and Heteroaryl-Phenyloxazolidinones"; WO 95/14684,
published 1 June 1995, "Esters of Substituted Hydroxyacetyl-Piperazine Phenyl
30 Oxazolidinones"; PCT/US96/05202, filed 18 April 1996, "Spirocyclic and Bicyclic
Diazinyl and Carbazinyl Oxazolidinones"; U.S. Patent Nos. 5,231,188 and 5,247,090,
"Tricyclic [6,6,5]-Fused Oxazolidinone Antibacterial Agents," WO 96/23788,
published 8 August 1996, "Hetero-Aromatic Ring Substituted Phenyloxazolidinone
Antimicrobials," and WO 94/13649, published 23 June 1994, "Tropone-Substituted
35 Phenyloxazolidinone Antibacterial Agents."

Nowhere do these patents, applications or publications teach or suggest N-

oxide oxazolidinone compounds.

INFORMATION DISCLOSURE

U.S. Patent No. 4,722,928 discloses N-oxide prodrug derivatives of 3-hydroxy morphinans and partial morphinans analgesics, agonist-antagonists, and narcotic antagonists, which are useful therapeutic entities providing enhanced bioavailability of these compounds from orally administered dosage forms. In contrast, there is no change in the bioavailability of the N-oxide compounds of the present invention.

This patent further states that there is no way to accurately predict which prodrug structure will be suitable for a particular drug. A derivative which may work well for one drug may not do so for another. Differences in the absorption, metabolism, distribution, and excretion among drugs do not permit generalizations to be made about prodrug design.

Chemical Abstracts 118:147331y (1993) discloses anti-cancer anthracene amine N-oxide prodrugs with low cytotoxicity which are bio-reduced within anaerobic neoplastic tissue to the cytotoxic amine anticancer agents. There is no suggestion that N-oxide prodrugs can be bio-reduced in normal tissue. These compounds are also potentially useful against anaerobic bacterial and protozoal infections.

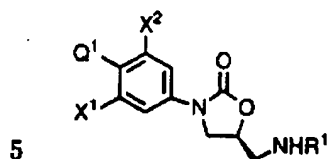
L.H. Patterson, "Rationale for the use of aliphatic N-oxides of cytotoxic anthraquinones as prodrug DNA binding agents: a new class of bio-reductive agent," *Cancer and Metastasis Review* 12:119-134 (1993) discloses that such N-oxides are not intrinsically cytotoxic. It further states that investigations into the fate of N-oxide administration to animals show that, in general, aliphatic N-oxides are stable *in vivo* and are recovered quantitatively following intravenous dosing. Hence, the article concludes that it would appear that aliphatic N-oxides are not metabolised in oxygenated tissue to any significant extent. In contrast, the aliphatic N-oxide compounds of the present invention are surprisingly and unexpectedly reduced back to the parent amine very rapidly *in vivo*.

The problem in the art is difficulty in formulating the parent amine compounds for intravenous and injectable use. The N-oxide compounds of the present invention have high water solubility and are readily formulated in aqueous vehicles.

SUMMARY OF THE INVENTION

The present invention particularly provides:

A compound of the formula I



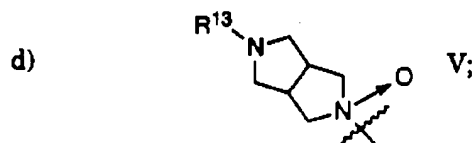
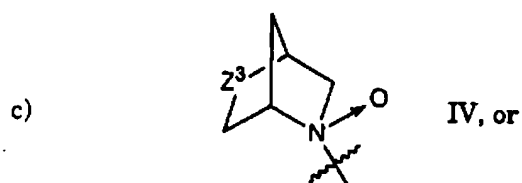
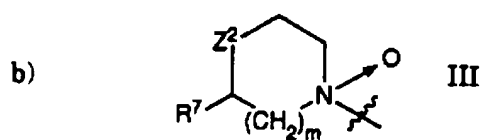
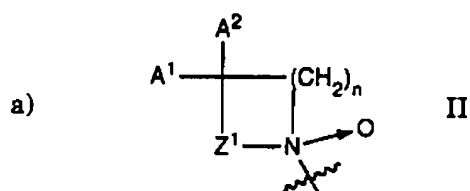
wherein X^1 and X^2 are independently

-H,

-F, or

10 -Cl;

wherein Q^1 is:



wherein Z^1 is

a) $-CH_2-$, or

b) $-CH(R^5)-CH_2-$;

35 wherein Z^2 is

a) $-O_2S-$,

b) -O-, or

c) -N(R⁸)-;wherein Z³ isa) -O₂S-, or

5 b) -O-;

wherein A¹ is

a) H-, or

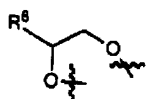
b) CH₃-;wherein A² is

10 a) H-,

b) HO-,

c) CH₃CO₂-,d) CH₃-,e) CH₃O-,15 f) R²O-CH₂-C(O)-NH-g) R³O-C(O)-NH-,h) R⁴-C(O)-NH-,i) (C₁-C₂)alkyl-O-C(O)-, orj) HO-CH₂-; or20 A¹ and A² taken together are:

a)



or

25 b) O=

;

wherein R¹ is

a) -CHO,

b) -COCH₃,30 c) -COCHCl₂,d) -COCHF₂,e) -CO₂CH₃,f) -SO₂CH₃, org) -COCH₂OH;35 wherein R² is

a) H-,

- b) CH_3 -,
- c) phenyl- CH_2 -, or
- d) $\text{CH}_3\text{C(O)}$ -;

wherein R^3 is

- 5 a) $(\text{C}_1\text{-C}_3)\text{alkyl}$ -, or
- b) phenyl-;

wherein R^4 is

- a) H-,
- b) $(\text{C}_1\text{-C}_4)\text{alkyl}$,
- 10 c) aryl $-(\text{CH}_2)_p$,
- d) ClH_2C -,
- e) Cl_2HC -,
- f) FH_2C -,
- g) F_2HC -, or
- 15 h) $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$;

wherein R^5 is

- a) H-, or
- b) $(\text{C}_1\text{-C}_3)\text{alkyl}$;

wherein R^6 is

- 20 a) H-, or
- b) HOH_2C ;

wherein R^7 is

- a) H-, or
- b) H_3C ;

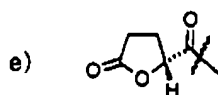
25 wherein R^8 is

- a) $\text{R}^2\text{O-C(R}_{10})(\text{R}_{11})\text{-C(O)}$ -,
- b) $\text{R}^3\text{O-C(O)}$ -,
- c) $\text{R}^4\text{-C(O)}$ -,

30



VI

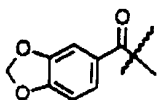


VII

35

f) $\text{H}_3\text{C}-\text{C}(\text{O})-(\text{CH}_2)_2-\text{C}(\text{O})-$,

g) R^9-SO_2- ,

h)  VIII, or

5

i) $\text{R}^{12}-\text{NH}-\text{C}(\text{O})-$;

wherein R^9 is

a) $-\text{CH}_3$,

10 b) $-\text{CH}_2\text{Cl}$

c) $-\text{CH}_2\text{CH}=\text{CH}_2$,

d) aryl, or

e) $-\text{CH}_2\text{CN}$;

wherein R^{10} and R^{11} are independently

15 a) $\text{H}-$,

b) CH_3- ; or

R^{10} and R^{11} taken together are $-\text{CH}_2-\text{CH}_2-$;

wherein R^{12} is $-(\text{CH}_2)_p$ -aryl;

wherein R^{13} is

20 a) $\text{R}^2\text{O}-\text{C}(\text{R}_{10})(\text{R}_{11})-\text{C}(\text{O})-$,

b) $\text{R}^3\text{O}-\text{C}(\text{O})-$,

c) $\text{R}^4-\text{C}(\text{O})-$,

d) R^9-SO_2- , or

e) $\text{R}^{12}-\text{NH}-\text{C}(\text{O})-$;

25 wherein m is zero (0) or one (1);

wherein n is one (1) to three (3), inclusive;

wherein p is zero (0) or one (1);

wherein aryl is phenyl substituted with zero (0) or one (1) of the following:

a) $-\text{F}$,

30 b) $-\text{Cl}$,

c) $-\text{OCH}_3$,

d) $-\text{OH}$,

e) $-\text{NH}_2$,

f) $-(\text{C}_1-\text{C}_4)\text{alkyl}$,

35 g) $-\text{O}-\text{C}(\text{O})-\text{OCH}_3$,

h) $-\text{NO}_2$, or

i) -CN;

with the following provisos:

1) in the moiety of formula II, Z^1 is $-\text{CH}(\text{R}^5)-\text{CH}_2-$ wherein R^5 is $(\text{C}_1-\text{C}_3)\text{alkyl}$, only when n is one (1), A^1 is H and A^2 is $\text{R}^2\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$, $\text{R}^3\text{O}-\text{C}(\text{O})-\text{NH}-$, or $\text{R}^4-\text{C}(\text{O})-\text{NH}-$; and

2) in the moiety of formula II, when Z^1 is $-\text{CH}_2-$, n is one (1).

The present invention more particularly provides:

The compound of claim 1 wherein Q^1 is the moiety of formula II;

The compound of claim 1 wherein Q^1 is the moiety of formula III;

10 The compound of claim 1 wherein Q^1 is the moiety of formula IV;

The compound of claim 1 wherein Q^1 is the moiety of formula V;

The compound of claim 1 wherein one of X^1 and X^2 is $-\text{H}$ and the other is $-\text{F}$ or wherein X^1 is $-\text{F}$ and X^2 is $-\text{F}$; and

The compound of claim 1 wherein R^1 is acetyl.

15 The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, $(\text{C}_1-\text{C}_3)\text{alkyl}$ refers to alkyl of one to three carbon atoms, inclusive, or methyl, ethyl, propyl and isopropyl, straight and branched forms thereof.

Throughout this application, abbreviations which are well known to one of ordinary skill in the art may be used, such as "Ph" for phenyl, "Me" for methyl, and "Et" for ethyl.

The following Charts I-IX describe the preparation of the parent amine compounds, which are the starting compounds from which the N-oxide compounds of the present invention are prepared. All of the starting compounds are prepared by procedures described in these charts or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. The following applications and publications which further describe and exemplify these procedures are hereby incorporated by reference herein: WO 95/07271, published 16 March 1995; WO96/15130, published 23 May 1996; WO 95/25106, published 21 September 1995; WO96/13502, published 9 May 1996; WO 93/23384, published 25 November 1993; WO 95/4684, published 1 June 1995; and PCT/US96/05202, filed 18 April 1996.

In the text below corresponding to these charts, the formula at the left margin corresponds to a specific Q^2 moiety in the charts and the other variables are as defined with X^1 and X^2 most often being hydrogen or fluorine and R^1 most often being $-\text{COCH}_3$, for purposes of example only.

5

CHART I

- I-A Using the procedures from WO 95/07271, published 16 March 1995, page 21, line 33, thru page 23, line 32 for preparation of the intermediate sulfide and then oxidation to the sulfone using the general procedures from WO 95/07271, published 16 March 1995, page 15, line 32 thru page 16, line 14.
- 10 I-B Using the procedures described in WO 95/07271, published 16 March 1995, page 21, line 33, thru page 23, line 32, but substituting oxazolidine for thiazolidine.

CHART II

- 15 II-A Using the general procedures from WO 95/07271, published 16 March 1995, page 12, line 31, thru page 16, line 14.
- II-B Using the general procedures from WO 95/07271, published 16 March 1995, page 12, line 31 thru page 16, line 14, but substituting 2-methylthiomorpholine for thiomorpholine. 2-Methylthiomorpholine is prepared according to the procedure of Gallego, *et al*, *J. Org. Chem.*, 1993, 58, 3905-11.
- 20 II-C Using the general procedures from WO96/15130, published 23 May 1996, Examples 2 and 3 at page 14, line 24, thru page 17, line 21.

CHART III

- 25 III-A Using the general procedures from WO 95/07271, published 16 March 1995, page 19, line 6, thru page 21, line 13; and page 23, line 33, thru page 24, line 35.
- III-B Using the general procedures from WO96/15130, published 23 May 1996, Example 1 at page 12, line 1, thru page 14, line 22.

CHART IV

- 30 IV-A Using the general procedures from WO 95/25106, published 21 September 1995, page 20, line 27 thru page 22, line 5 but substituting azetidine for piperidine.
- IV-B Using the general procedures of WO96/13502, published 9 May 1996, Example 11 at page 53, line 32 through page 56, line 3, but substituting 1-
- 35 (diphenylmethyl)-3-azetidinone in place of 1-benzyl-3-pyrrolidinone. 1-(Diphenylmethyl)-3-azetidinone can be prepared by the procedure of

Chatterjee, et al, *Synthesis*, 1973, 153-4.

- IV-C From IV-B using the general procedure from WO96/13502, published 9 May 1996, page 56, line 4 through line 17.
- 5 IV-D From IV-C using the general procedure from WO 95/25106, published 21 September 1995, page 28, line 26 through page 29, line 5.
- IV-E Using the general procedures from WO96/13502, published 9 May 1996, Example 2 at page 33, line 4, thru page 36, line 22.
- IV-F Starting with IV-E, and using procedures well known for acetylation; e.g., acetic anhydride and triethylamine in a suitable solvent.
- 10 IV-G Using the general procedures from WO96/13502, published 9 May 1996, Example 7 at page 43, line 36, thru page 47, line 28.
- IV-H Using the general procedures from WO96/13502, published 9 May 1996, Example 6 at page 40, line 31, thru page 43, line 34.
- IV-I Using the procedures of WO96/13502, published 9 May 1996, Example 1 at
15 page 29, line 25 thru page 33, line 2.
- IV-J Wherein R^2 is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13 at page 56, line 19 thru page 59, line 4, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride. 3-Acetylaminoazetidine
20 hydrochloride is prepared by the procedure of Nisato, et al., J. Heterocycl. Chem. 1985, 22, 961-3.
- IV-J Wherein R^2 is methyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of
25 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting methoxyacetyl chloride in place of benzyloxyacetyl chloride.
- IV-J Wherein R^2 is benzyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of
30 3-(trifluoroacetylamino)pyrrolidine hydrochloride.
- IV-J Wherein R^2 is acetyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of
35 acetoxycetyl chloride in place of benzyloxyacetyl chloride.
- IV-K Wherein R^3 is methyl, ethyl, propyl, or phenyl; using the procedure

- described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoozetidine hydrochloride in place of 3-(trifluoroacetyl-amino)pyrrolidine hydrochloride and substituting methyl, ethyl, propyl, or phenyl chloroformate in place of benzyloxyacetyl chloride.
- 5 IV-L Wherein R⁴ is hydrogen; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoozetidine hydrochloride in place of 3-(trifluoroacetylaminoozetidine hydrochloride and substituting methyl
- 10 formate in place of benzyloxyacetyl chloride.
- IV-L Wherein R⁴ is all others listed; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoozetidine hydrochloride in place of 3-(trifluoroacetylaminoozetidine hydrochloride and substituting the appropriate acid chloride in place of benzyloxyacetyl
- 15 chloride.
- IV-M Using the general procedures of WO96/13502, published 9 May 1996, Example 1, Steps 2 thru 7, at page 30, line 14 thru page 33, line 2, but substituting methyl N-benzylazetidine-3-carboxylate in place of 1-(diphenyl-methyl)-3-methoxyazetidine. Methyl N-benzylazetidine-3-carboxylate can be
- 20 prepared by the procedure of Mason, et al, EP 169602 A1.
- IV-N Starting with IV-M and using the general procedures of WO 95/25106, published 21 September 1995, page 22, line 11 through line 20.

CHART V

- 25 V-A Using the procedure from WO 95/25106, published 21 September 1995, page 20, Example 1, but using pyrrolidine instead of piperidine.
- V-B Using the procedures of WO96/13502, published 9 May 1996, Example 11 at page 53, line 32, thru page 56, line 3.
- V-C From V-B, following the procedure of WO96/13502, published 9 May 1996, page 56, lines 4 through 17.
- 30 V-D From V-C, using the general procedure of WO 95/25106, published 21 September 1995, page 28, line 26, thru page 29, line 5.
- V-E Using the procedures described in WO96/13502, published 9 May 1996, Example 10 at page 50, line 25, thru page 53, line 30. Or, from V-C by
- 35 reduction using methods well known in the art such as sodium borohydride in methanol.

- V-F From V-E using standard acetylation procedures; e.g., acetic anhydride in pyridine.
- V-G As described in WO96/13502, published 9 May 1996, Example 7 at page 43, line 36, thru page 47, line 28 but substituting 1-benzyl-3-methyl-3-pyrrolidinol hydrochloride for 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride. 1-Benzyl-3-methyl-3-pyrrolidinol hydrochloride can be prepared from 1-benzyl-3-pyrrolidinone by methods known in the art, eg, reaction with methylmagnesium bromide and treatment of the product with one equivalent of hydrochloric acid. 1-Benzyl-3-pyrrolidinone is commercially available.
- V-H Using the general procedures of WO96/13502, published 9 May 1996, Example 6 at page 40, line 31 through page 43, line 34, but substituting 1-benzyl-3-methyl-3-pyrrolidinol hydrochloride (prepared as described above) in place of 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride.
- V-I As described in WO96/13502, published 9 May 1996, Example 1 at page 29, line 25, thru page 33, line 2, but substituting commercially available 1-benzyl-3-pyrrolidinol for 1-(diphenylmethyl)-3-azetidinol.
- V-J Wherein R^2 is H and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13 at page 56, line 19, thru page 59, line 4;
- V-J Wherein R^2 is methyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methoxyacetyl chloride for benzyloxyacetyl chloride.
- V-J Wherein R^2 is benzyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27.
- V-J Wherein R^2 is acetyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting acetoxyacetyl chloride for benzyloxyacetyl chloride.
- V-J Where R^2 is H and R^5 is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15 at page 62, lines 5-28.
- V-J Wherein R^2 is benzyl and R^5 is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15, Step 1, at page 62, lines 5-19.

- V-J Wherein R^2 is methyl or acetyl and R^5 is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15, Step 1, at page 62, lines 5-19, but substituting methoxyacetyl chloride or acetoxyacetyl chloride for benzyloxyacetyl chloride.
- 5 V-J Wherein R^5 is other alkyl; using the general procedures described above but substituting other 4-alkyl-3-aminopyrrolidines in place of 3-amino-4-methylpyrrolidine.
- 10 V-K Wherein R^3 is methyl, ethyl, propyl or phenyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methyl chloroformate, ethyl chloroformate, propylchloroformate, or phenylchloroformate for benzyloxyacetyl chloride.
- 15 V-K Wherein R^3 is methyl, ethyl, propyl, or phenyl and R^5 is methyl; by reaction of (S)-(N)-[[[3-fluoro-4-(3-amino-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide with the appropriate chloroformate. The above amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.
- 20 V-K Wherein R^5 is other alkyl; From the appropriate amine and chloroformate. The amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29, but starting with other 3-alkyl-4-aminopyrrolidines in place of 4-amino-3-methylpyrrolidine.
- 25 V-L Where R^4 is H and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methyl formate in place of benzyloxyacetyl chloride.
- 30 V-L Where R^4 is all others listed and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.
- 35 V-L Where R^4 is H and R^5 is methyl; by reaction of formic acid and dicyclohexylcarbodiimide. The required amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.
- 35 V-L Where R^4 is all others and R^5 is methyl; by reaction of (S)-(N)-[[[3-fluoro-4-(3-amino-4-methylpyrrolidinyl)phenyl]-2-oxo-5-

oxazolidinyl)methyl]acetamide with the appropriate acid chloride. The required amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.

- 5 V-L Where R⁵ is other alkyl; Using the above procedures, but starting with other 3-alkyl-4-aminopyrrolidines in place of 4-amino-3-methylpyrrolidine.
- V-M Using the general procedure from WO 95/25106, published 21 September 1995, page 22, lines 6 through 12, 5, but using pyrrolidine-3-carboxylic acid methyl ester instead of piperidine-4-carboxylic acid ethyl ester. Pyrrolidine-3-carboxylic acid methyl ester is prepared by the procedure of Morgans, et al, *Tetrahedron Lett.*, 1979, 1959.
- 10 V-N From V-M, using the general procedure of WO 95/25106, published 21 September 1995, page 22, lines 12 through 20.

CHART VI

- 15 VI-A Using the general procedures from WO 95/25106, published 21 September 1995, page 20, line 27, thru page 22, line 5.
- VI-B Using the procedure of WO 95/25106, published 21 September 1995, WO 95/25106, published 21 September 1995, page 22, line 21 thru line 26.
- VI-C From VI-B, using the procedure from WO 95/25106, published 21 September 1995, page 22, lines 27 through 35.
- 20 VI-D From VI-C, using the procedure from WO 95/25106, published 21 September 1995, page 28, line 26 thru page 29, line 5.
- VI-E Prepared from VI-C by reduction via standard procedures known in the art; eg, sodium borohydride in methanol.
- 25 VI-F Prepared from VI-E by procedures known in the art; eg, acetic anhydride and triethylamine.
- VI-G Using the procedures from WO96/13502, published 9 May 1996, Example 7, page 43, line 36 thru page 47, line 28 but substituting commercially available 4-hydroxy-4-methylpiperidine for 3-hydroxy-3-methylazetidine.
- 30 VI-H Using the procedures from WO 95/25106, published 21 September 1995, page 20, line 27 thru page 22, line 5, but substituting 4-methoxy-4-methylpiperidine in place of piperidine. 4-Methoxy-4-methylpiperidine can be prepared according to the procedure of McManus, et al, *J. Med. Chem.*, 1965, 8, 766-776.
- 35 VI-I Using the procedures from WO 95/25106, published 21 September 1995, page 20 line 27 thru page 22, line 5, but substituting 4-methoxypiperidine

for piperidine. 4-Methoxypiperidine can be made by the procedure of McManus, et al, *J. Med. Chem.*, 1965, 8, 766-776.

- VI-J Wherein $R^2 = H$; Prepared by reaction of (S)-N-[[3-[4-(4-aminopiperidinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared according to the procedures of WO 95/25106, published 21 September 1995, page 22, line 36 thru page 23, line 24) with acetoxyacetyl chloride and triethylamine followed by hydrolysis of the acetoxy group with methanolic potassium carbonate.
- 5
- VI-J Wherein $R^2 = \text{methyl}$; prepared by reaction of the starting material of VI-J ($R^2 = H$) with methoxyacetyl chloride and triethylamine.
- 10
- VI-J Wherein R^2 is benzyl; prepared by reaction of the starting material of VI-J ($R^2 = H$) with benzyloxyacetyl chloride and triethylamine.
- VI-J Wherein R^2 is acetyl; prepared by reaction of the starting material of VI-J ($R^2 = H$) with acetoxyacetyl chloride and triethylamine.
- 15
- VI-K Wherein R^3 is methyl, ethyl, propyl, or phenyl; prepared by reaction of the starting material of VI-J ($R^2 = H$) with methyl-, ethyl-, propyl-, or phenylchloroformate.
- VI-L Wherein $R^4 = H$; By reaction of the starting material of VI-J ($R^2 = H$) with methylformate.
- 20
- VI-L Wherein $R^4 = \text{all others listed}$; By reaction of the starting material of VI-J ($R^2 = H$) with the appropriate acid chloride.
- VI-M Using the procedure from WO 95/25106, published 21 September 1995, page 22, line 6 thru line 12.
- VI-N Using the procedure from WO 95/25106, published 21 September 1995, page 22, lines 12 through 20.
- 25

CHART VII

- VII-A Using the general procedures of WO 95/25106, published 21 September 1995, page 20, line 27 through page 22, line 5, but substituting commercially available azepine in place of piperidine.
- 30
- VII-B Using the procedure of WO 95/25106, published 21 September 1995, page 22, line 21 thru line 26 but substituting 1,4-dioxo-8-aza-spiro[4.6]undecane for 1,4-dioxo-8-aza-spiro[4.5]decane. 1,4-Dioxo-8-aza-spiro[4.6]undecane can be prepared by the procedure of R. A. Johnson, et al, *J. Org. Chem.*, 1968, 33, 3187-3195.
- 35
- VII-C From VII-B, following the procedure of WO96/13502, published 9 May 1996, page 56, lines 4 through 17.

- VII-D From VII-C using the general procedure of WO 95/25106, published 21 September 1995, page 28, line 26, thru page 29, line 5.
- VII-E Prepared from VII-C by reduction via standard procedures known in the art; eg, sodium borohydride in methanol.
- 5 VII-F Prepared from VII-E by procedures known in the art; eg, acetic anhydride and triethylamine.
- VII-G Using the procedures from WO96/13502, published 9 May 1996, Example 7, page 43, line 36 thru page 47, line 28 but substituting 4-hydroxy-4-methyl-azepine for 3-hydroxy-3-methylazetidione. 4-Hydroxy-4-methylazepine can
10 be prepared by the procedure of Grob, et al, *Helv. Chim. Acta*, 1962, 45, 1823-1830.
- VII-H Using the general procedures of WO96/13502, published 9 May 1996, Example 6, page 40, line 31 through page 43, line 34, but substituting 1-benzyl-4-methyl-4-azepinol in place of 1-(diphenylmethyl)-3-methyl-3-
15 azetidinol hydrochloride. 1-Benzyl-4-methyl-4-azepinol can be prepared by the reaction of methyl magnesium bromide with 1-benzyl-4-azepinone. 1-Benzyl-4-azepinone can be prepared by the procedure of Casy, et al, *J. Chem. Soc.* 1964, 5130-5132.
- VII-I As described in WO96/13502, published 9 May 1996, Example 1, at page 29,
20 line 25, thru page 33, line 2, but substituting 1-benzyl-4-azepinol for 1-(diphenylmethyl)-3-azetidinol. 1-Benzyl-4-azepinol can be prepared by the procedure of S. Sakanoue, et al, *Chem. Pharm. Bull.*, 1990 38, 2981-2985.
- VII-J Wherein R^2 is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13, page 56, line 19, thru page 59, line 4 but
25 substituting 4-(trifluoroacetyl amino)azepine in place of 3-(trifluoroacetyl amino)pyrrolidine. 4-(Trifluoroacetyl amino)azepine can be prepared by reaction of 1-benzyl-4-azepinamine with trifluoroacetic anhydride in a suitable solvent such as chloroform, followed by removal of the benzyl protecting group via hydrogenolysis using palladium on carbon
30 as a catalyst in a solvent such as ethyl acetate. 1-Benzyl-4-azepinamine can be prepared by the procedure of Morosawa, et al, *Bull. Chem. Soc. Jpn.*, 1958, 31, 418-422.
- VII-J Wherein R^2 is methyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line
35 27, but substituting 4-(trifluoroacetyl amino)azepine for 4-(trifluoroacetyl amino)pyrrolidine and substituting methoxyacetyl chloride in

place of benzyloxyacetyl chloride.

- 5
VII-J Wherein R^2 is benzyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetyl-amino)azepine for 4-(trifluoroacetyl-amino)pyrrolidine.
- 10
VII-J Wherein R^2 is acetyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetyl-amino)azepine for 4-(trifluoroacetyl-amino)pyrrolidine and substituting acetoxyacetyl chloride in place of benzyloxyacetyl chloride.
- VII-K Wherein R^3 is methyl, ethyl, propyl, or phenyl; prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (prepared as an intermediate in the synthesis of VII-J) with the appropriate chloroformate and triethylamine in chloroform.
- 15 VII-L Wherein R^4 is H; Prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared as an intermediate in the synthesis of VII-J) with formic acid according to the general procedure of WO 93/23384, published 25 November 1993, page 23, lines 4-17.
- 20 VII-L Wherein R^4 is all others; Prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared as an intermediate in the synthesis of VII-J) with the appropriate acid chloride and triethylamine.
- 25 VII-M Using the procedure from WO 95/25106, published 21 September 1995, page 22, line 6 thru line 12, but substituting azepine-4-carboxylic acid ethyl ester in place of piperidine-4-carboxylic acid ethyl ester. Azepine-4-carboxylic acid ethyl ester can be prepared from azepine-4-carboxylic acid by normal procedures known in the art, eg, reaction with ethanol and hydrochloric acid. Azepine-4-carboxylic acid can be prepared by the procedure of
- 30 Krogsgaard-Larsen, et al, *Eur. J. Med. Chem. Chim. Ther.*, 1979, 14, 157-164.
- VII-N From VII-M, using the general procedure of WO 95/25106, published 21 September 1995, page 22, lines 12 through 20.
- 35 VIII-A Wherein $R^2 = H$; According to the procedure of WO 95/14684, published 1 June 1995, page 9, lines 1-28.

CHART VIII

- VIII-A Wherein R^2 = methyl; According to the general procedures of WO 93/23384, published 25 November 1993, page 19, lines 26- 33.
- VIII-A Wherein R^2 = benzyl; According to the procedure of WO 95/14684, published 1 June 1995, page 9, lines 1-14.
- 5 VIII-A Wherein R^2 = acetyl; According to the procedure of WO 95/14684, published 1 June 1995, page 28, lines 24-35.
- VIII-B Wherein R^3 = Me, Et, Pr, or Ph; Using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28 and substituting methyl-, ethyl, propyl, or phenylchloroformate as appropriate.
- 10 VIII-C Wherein R^4 = H; Using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 4-17.
- VIII-C Wherein R^4 = all others; Using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 19-28, and substituting the appropriate acid chloride for methylchloroformate.
- 15 VIII-D Prepared according to the general procedure found in WO 93/23384, published 25 November 1993, page 25, lines 13-25.
- VIII-E Prepared according to the general procedure from WO 93/23384, published 25 November 1993, page 25, lines 13-25, but substituting commercially available 5-oxo-2-tetrahydrofurancarboxylic acid in place of (R)-2-tetrahydrofuranoic acid.
- 20 VIII-F Prepared according to the procedure of WO 93/23384, published 25 November 1993, page 18, lines 10-17.
- VIII-G Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate sulfonyl chloride using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28. Methyl, chloromethyl, allyl, and substituted arylsulfonyl chlorides are commercially available. Cyanomethylsulfonyl chloride can be prepared according to the procedure of M. P. Sammes, et al, *J. Chem. Soc. (C)*, 1971, 2151-2155.
- 25 VIII-H Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and piperonyl chloride using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28. Piperonyl chloride is commercially available.
- 30 VIII-I Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate carboxylic acid using the general procedure of WO 95/14684, published 1 June 1995, page 10,
- 35

lines 4-17. The acids are commercially available.

VIII-J Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and the appropriate isocyanate. The required isocyanates are commercially available.

5

CHART IX

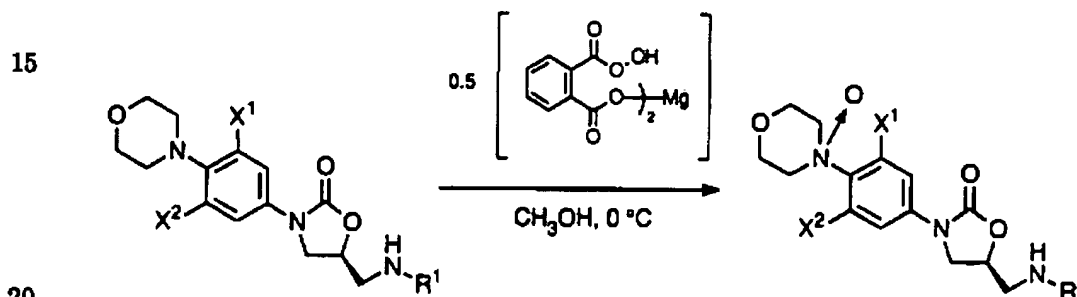
- IX-A Wherein R^2 is H; Prepared according to the procedures of PCT/US96/05202, filed 18 April 1996, Examples 1, 2 and 3, page 12, line 11 through page 15, line 7.
- IX-A Wherein R^2 is methyl; Prepared according to the general procedures of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting methoxyacetyl chloride for benzyloxyacetyl chloride.
- IX-A Wherein R^2 is benzyl; Prepared according to the procedures of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32.
- IX-A Wherein R^2 is acetyl; Prepared according to the general procedures of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting acetoxyacetyl chloride for benzyloxyacetyl chloride.
- IX-B Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate chloroformate for benzyloxyacetyl chloride.
- IX-C Wherein R^4 is H; Prepared from (S)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 4-16.
- IX-C Wherein R^4 is all others listed; Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.
- IX-D Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate sulfonyl chloride in place of benzyloxyacetyl chloride. The sulfonyl chlorides can be obtained as described for VIII-G.
- IX-E Prepared from (S)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) and the appropriate carboxylic acid using the general procedures of WO 93/23384, published 25 November 1993,

page 18, lines 10-17. The appropriate carboxylic acids are commercially available.

IX-F Prepared by combining (S)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) and the appropriate isocyanate. The required isocyanates are commercially available.

GENERAL PROCEDURE:

The compounds of this invention are prepared by oxidation of a suitable precursor amine with any of a variety of oxidizing agents. Suitable oxidants include pertrifluoroacetic acid, meta-chloroperbenzoic acid (MCPBA), and magnesium monoperoxyphthalate (MMPP). For example, the synthesis is shown below for the case wherein Q¹ is morpholine and the oxidant is MMPP.



Oxidation of any of the oxazolidinones of Charts I-IX in which Q² is any of the other groups previously described is carried out similarly.

Charts X-XVIII show the final N-oxide compounds of the present invention which are prepared from the parent amines of Charts I-IX, respectively, by using the above General Procedures.

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that alternative synthetic processes are known to one of ordinary skill in organic chemistry.

The compounds of the present invention have an advantage over the parent amines in being exceedingly water soluble (see Table 1 below). For example, the compound of Example No. 2 has a solubility of 409 mg/ml. The parent amine has a water solubility of only 3.7 mg/ml. The N-oxide compounds of the present invention also retain all the *in vitro* and *in vivo* activities of the parent amines. The enhanced water solubility makes the N-oxide compounds of the present invention ideal for intravenous or injectable formulations.

Table 1. Solubility Data for the N-oxides and parent amines.

Example Number	Parent Amine Solubility (mg/mL)	N-Oxide Solubility (mg/mL)
1	4.2	348
2	3.7	534
3	0.28	12.9
6	0.031	1.1

Procedure for Measuring Solubility:

In all solubility studies, an excess of compound is added to 0.5 to 1 ml of pH 7, 50 mM phosphate buffer or other vehicle of interest. The samples are capped and stirred via magnetic stir bars for 24 to 48 hours at room temperature. Samples are filter centrifuged (800 x g) for 5-10 minutes through Millipore Ultrafree-MC 0.22 micron filter units. The supernate is analyzed by either UV or HPLC to quantitate the drug concentration. Results of the solubility testing of the compounds of the present invention are given above in Table 1.

The oxazolidinone compounds of the present invention have useful activity against a variety of microorganisms. The *in vitro* activity of compounds of the present invention are assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically" (MFT) published January 1993 by the National Committee for Clinical Laboratory Standards (NCCLS), 771 East Lancaster Avenue, Villanova, Pennsylvania 19084, USA. The activity of selected compounds of the present invention against *Staphylococcus aureus* and *Streptococcus pneumoniae* are shown in Table 2.

Table 2. Activity of the N-oxides against *S. Aureus* and *S. Pneumoniae*.

Example Number	MIC ($\mu\text{g/mL}$) <i>S. Aureus</i> UC® 9213	MIC ($\mu\text{g/mL}$) <i>S. Pneumoniae</i> UC® 9912
1	2	0.5
2	4	1
3	4	1
4	2	0.5
5	4	0.5
6	2	0.25

As such, the compounds of the present invention are useful for treating microbial infections in humans or other warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I. The compound is administered in a pharmaceutical composition orally, parenterally (such as subcutaneously or intravenously), or topically. Preferably the compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

The following compounds of the present invention (with cross-references to the formulas in the charts below) are preferred:

- X-A $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-(1,1-dioxothiazolidin-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- X-B $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-(3-oxazolidinyl)]phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide N-oxide.
- XI-A $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-(1,1-dioxothiomorpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XI-C $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-[(1S,4S)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XII-A $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{F}$: (S)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide.

- XII-A $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XII-A $R^1 = \text{COCH}_2\text{OH}$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]hydroxyacetamide N-oxide.
- 5 XII-A $R^1 = \text{CHO}$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]formamide N-oxide.
- XII-A $R^1 = \text{CO}_2\text{CH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]methylcarbamate N-oxide.
- XII-A $R^1 = \text{COCH}_2\text{Cl}_2$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]dichloroacetamide N-oxide.
- 10 XII-B $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XIII-C $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- 15 XIII-H $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XIII-K $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^3 = \text{CH}_3$: (S)-N-[[3-[3-fluoro-4-[3-[(methoxycarbonyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- 20 XIII-J $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-[3-[(hydroxyacetyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XIV-E $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-Fluoro-4-(3-hydroxypyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- 25 XIV-J $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^2 = \text{H}$, $R^5 = \text{CH}_3$: (S)-N-[[3-[3-Fluoro-4-(cis-3-(hydroxyacetyl)amino)-4-methylpyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XIV-K $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^3 = \text{CH}_3$, $R^5 = \text{CH}_3$: (S)-N-[[3-[3-Fluoro-4-(trans-3-(methoxycarbonyl)amino)-4-methylpyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- 30 XV-B $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[3-[4-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.
- XV-D $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.
- 35

- XV-M $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-1-[4-[5-(acetylaminoethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-piperidine-4-carboxylic acid ethyl ester N-oxide.
- 5 XV-N $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[3-[3-fluoro-4-(4-hydroxymethyl)-piperidin-1-yl]-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.
- XVI-C $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[3-[3-fluoro-4-(4-oxoazepin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.
- 10 XVII-B $R^1 = \text{COCH}_3$, $X^1 = \text{H}$, $X^2 = \text{H}$, $R^3 = \text{CH}_3$: (S)-4-[4-[5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl]phenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.
- XVII-B $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^3 = \text{CH}_2\text{CH}_3$: (S)-4-[4-[5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, ethyl ester N-oxide.
- 15 XVIII-A $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-[cis-3-(hydroxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide N-oxide.
- XVIII-C $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^4 = \text{cyclopropyl}$: (S)-N-[[3-[3-fluoro-4-[cis-3-[(cyclopropyl)carbonyl]-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- 20 XVIII-D $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$, $R^9 = \text{CH}_3$: (S)-N-[[3-[3-fluoro-4-[cis-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XVII-A $R^1 = \text{COCH}_3$, $R^2 = \text{H}$, $X^1 = X^2 = \text{F}$: (S)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- 25 XVII-A $R^1 = \text{COCH}_3$, $R^2 = \text{H}$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.
- XVII-B $R^1 = \text{COCH}_3$, $R^3 = \text{CH}_3$, $X^1 = X^2 = \text{F}$: (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.
- 30 XVII-B $R^1 = \text{COCH}_3$, $R^3 = \text{CH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

The following compounds of the present invention (with cross references to the formulas in the charts below) are most preferred:

- 35 XII-A $R^1 = \text{COCH}_3$, $X^1 = X^2 = \text{F}$: (S)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;

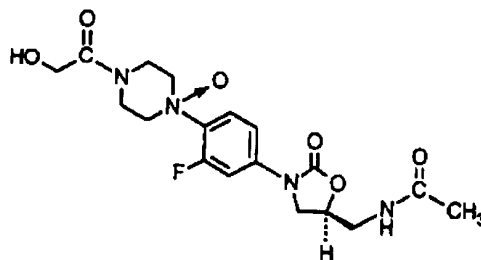
- XII-A $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide N-oxide;
- XVII-A $R^1 = \text{COCH}_3$, $R^2 = \text{H}$, $X^1 = X^2 = \text{F}$: (S)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
- 5 XVII-A $R^1 = \text{COCH}_3$, $R^2 = \text{H}$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
- XVII-B $R^1 = \text{COCH}_3$, $R^3 = \text{CH}_3$, $X^1 = X^2 = \text{F}$: (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide;
- 10 XVII-B $R^1 = \text{COCH}_3$, $R^3 = \text{CH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$: (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

DESCRIPTION OF PREFERRED EMBODIMENTS

EXAMPLE 1. (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide

15

20



(S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (VIII-A, $R^1 = \text{COCH}_3$, $R^2 = \text{H}$, $X^1 = \text{F}$, $X^2 = \text{H}$) (11.8 g) is dissolved in 200 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 18.5 g) is added and the resulting suspension is stirred at 25°C for two hours. The reaction is filtered and the filtrate is concentrated to afford a white solid. This solid is chromatographed on silica gel using 20% methanol in chloroform as eluent to afford the N-oxide. Lyophilization of this material affords the purified product as a hydrate (9.5 g).

Physical characteristics are as follows:

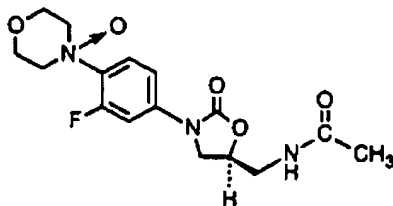
Mp 158-160 °C;

IR (mull) 3276, 3071, 1754, 1658, 1622, 1502, 1444, 1410, 1286, 1255, 1224, 1204, 1135, 1095, 752 cm^{-1} ;

MS (FAB) m/z 411, 565, 412, 411, 396, 395, 394, 393, 392, 335, 56.

EXAMPLE 2. (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide

5



10 (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (III-A, $R^1 = \text{COCH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$) (12.5 g) is suspended in 200 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 11.5 g) is added and the resulting suspension is stirred at 25°C for two hours. The reaction mixture is filtered and the filtrate is concentrated to afford a light-yellow solid. This material is chromatographed on silica gel using 10% methanol (saturated with ammonia) in chloroform as eluent to afford 8.75 g of the N-oxide.

Physical characteristics are as follows:

Mp 202-204 °C;

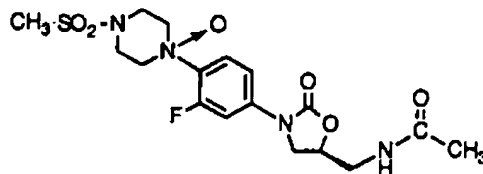
IR (mull) 1747, 1669, 1620, 1556, 1508, 1495, 1445, 1413, 1341, 1295, 1269,
20 1232, 1204, 1124, 755 cm^{-1} ;

MS (FAB) m/z 354, 708, 707, 355, 354, 339, 338, 337, 336, 86, 56.

Anal. Found: C, 53.99; H, 5.70; N, 11.76.

EXAMPLE 3. (S)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide

25



30 Pertrifluoroacetic acid is prepared in situ by the addition of 30% H_2O_2 solution (0.15 mL) to trifluoroacetic anhydride (0.45 mL) in 5 mL of methylene chloride at 0°C. This solution is stirred at 0°C for ten minutes, at 25°C for 30 minutes and then cooled back to 0 °C. (S)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (VIII-G, $R^1 = \text{COCH}_3$, $R^9 = \text{CH}_3$, $X^1 = \text{F}$, $X^2 = \text{H}$) (0.207 g) is added and the reaction is stirred at 25°C for 30 minutes and then concentrated. The residue is chromatographed on silica gel using

10% methanol (saturated with ammonia) in chloroform as the eluent to afford 0.14 g of the N-oxide as a hydrate.

Physical characteristics are as follows:

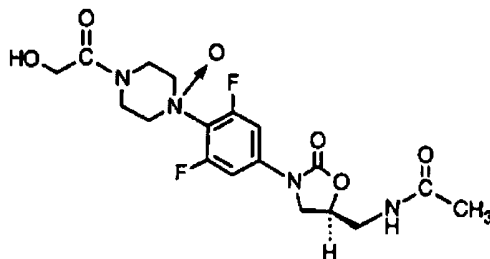
Mp 168-170 °C;

5 IR (mull) 1751, 1668, 1658, 1503, 1443, 1408, 1340, 1328, 1277, 1260, 1226, 1157, 1130, 1081, 855 cm⁻¹;

MS (FAB) *m/z* 431, 862, 861, 432, 431, 416, 415, 414, 413, 335, 56.

EXAMPLE 4. (S)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide.

10



15

(S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]- acetamide (VIII-A, R¹ = COCH₃, R² = H, X¹ = X² = F) (0.13 g) is dissolved in 5 mL of methanol. Monoperoxyphthalic acid, magnesium salt
 20 hexahydrate (80% pure, 0.2 g) is added and the resulting suspension is stirred at 25°C for 72 hours. An additional 0.2 g of monoperoxyphthalic acid is added and the reaction is stirred an additional 48 hours. The reaction mixture is filtered and the filtrate is concentrated to afford a light-yellow oil. This material is chromatographed on silica gel using 20% methanol (saturated with ammonia) in chloroform as eluent
 25 to afford 55 mg of the N-oxide.

Physical characteristics are as follows:

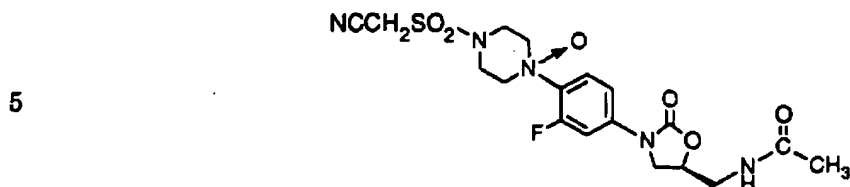
Mp 100-105 °C;

IR (mull) 3292, 1757, 1658, 1636, 1584, 1557, 1497, 1413, 1287, 1245, 1213, 1098, 1054, 1043, 1020 cm⁻¹;

30

MS (FAB) *m/z* 429 (M+H), 857, 429, 413, 412, 411, 353, 161, 145, 73, 56.

EXAMPLE 5. (S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.



(S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (VIII-G, $R^1 = \text{COCH}_3$, $R^9 = \text{NCCH}_2$, $X^1 = \text{F}$, $X^2 = \text{H}$) (0.550 g) is dissolved in 15 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.616 g) is added and the reaction is stirred at room temperature for 4 hours. The reaction is then filtered and the filtrate is concentrated to afford an oil. This oil is chromatographed on silica gel using 10% methanol (saturated with ammonia) in chloroform as eluent to afford 0.42 g of the N-oxide.

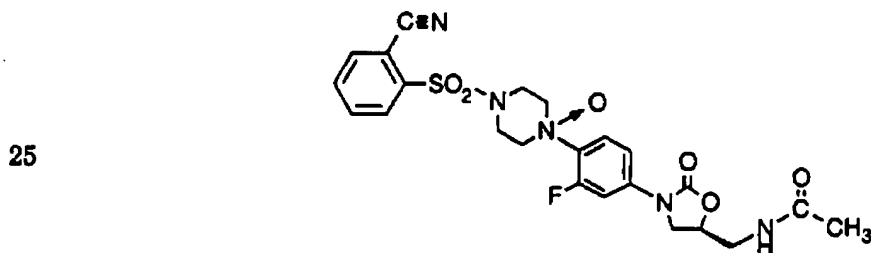
15 Physical characteristics are as follows:

Mp 153-156 °C.

IR (mull) 1748, 1656, 1625, 1503, 1443, 1406, 1357, 1342, 1257, 1224, 1161, 1148, 1137, 931, 756 cm^{-1} ;

MS (FAB) m/z 456 (M+H), 457, 456, 441, 440, 439, 438, 336, 335, 91, 56.

20 EXAMPLE 6. (S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.



(S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (VIII-G, $R^1 = \text{COCH}_3$, $R^9 = 2\text{-cyanophenyl}$, $X^1 = \text{F}$, $X^2 = \text{H}$) (0.5 g) is suspended in 10 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.616 g) is added and the reaction mixture is stirred at room temperature for 2 hours. The reaction is concentrated and the resulting oil is chromatographed on silica gel using 7% methanol (saturated with ammonia) in chloroform as eluent to afford 0.33 g of the N-oxide.

Physical characteristics are as follows:

Mp 190-192 °C.

IR (mull) 1756, 1678, 1661, 1620, 1500, 1486, 1408, 1280, 1256, 1222, 1181, 1168, 1129, 1082, 924 cm^{-1} ;

MS (FAB) m/z 518 (M+H), 520, 519, 518, 503, 502, 501, 500, 336, 335, 56.

5 EXAMPLE 7: Reduction of the N-oxide of Example 2 *in vivo* Following Intravenous and Oral Administration to Rats.

The rate and extent of reduction of the N-oxide of Example 2 was investigated *in vivo* using the following procedures: Six male Sprague-Dawley rats are used for this study. Three rats are given a single intravenous 10 mg/kg dose of the N-oxide and three rats are given a single oral 25 mg/kg dose of the N-oxide. Blood is collected pre-dose and up to 24 h post dose. The plasma is analyzed for the N-oxide and the parent amine by LC-MS.

Results:

15 Only traces of the N-oxide were found in plasma in the first time point immediately post intravenous injection. The parent amine was detected in plasma up to 10 h post dosing. The lower limit of quantitation for the assay was ≈ 0.01 $\mu\text{g/mL}$. Because the N-oxide was reduced to the parent amine so rapidly, pharmacokinetic parameters were measured for the parent amine rather than for the N-oxide.

20 After both intravenous and oral dosing of the N-oxide, the C_{max} , T_{max} and AUC values for the parent amine were very similar to those found when the parent amine compound was administered directly to rats using the same doses and protocol. The relative bioavailability of the parent amine from the orally administered N-oxide was approximately 100% when compared to orally
25 administered parent amine. The rapid and essentially quantitative conversion of the N-oxide to the parent amine *in vivo* demonstrates that the N-oxide is a suitable pro-drug for the parent amine.

FORMULA CHART

5

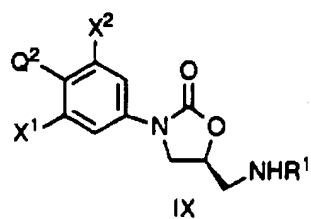
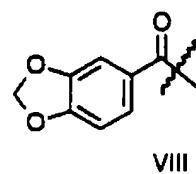
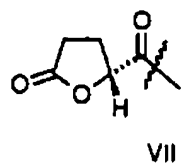
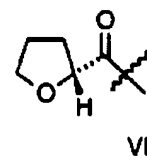
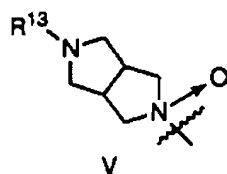
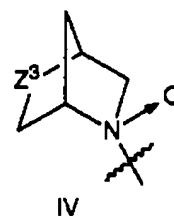
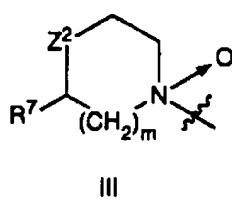
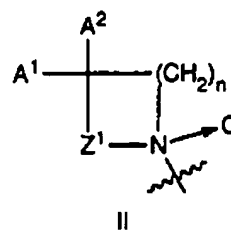
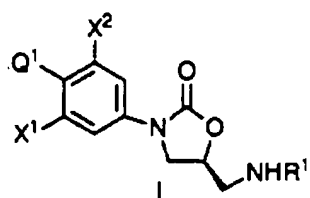
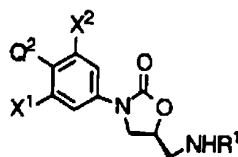


CHART I - THIAZOLIDINES

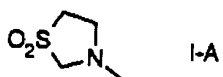
5



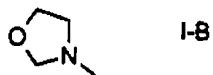
IX

wherein Q² is

10



I-A



I-B

15

wherein X¹ and X² are independently

-H,

-F, or

-Cl;

20 wherein R¹ is

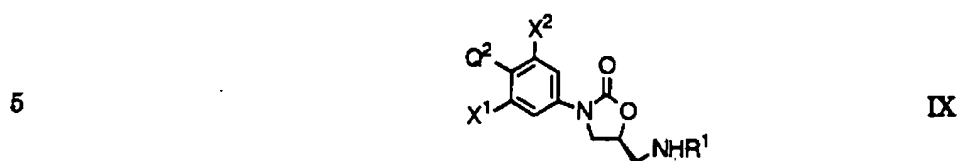
-CHO,

-COCH₃,-COCHCl₂,-COCHF₂,

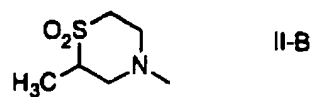
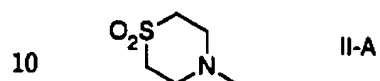
25

-CO₂CH₃,-SO₂CH₃, or-COCH₂OH.

CHART II - THIOMORPHOLINES - BRIDGED THIOMORPHOLINES



wherein Q² is



wherein X¹ and X² are independently

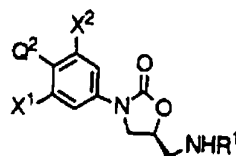
- 20
- H,
 - F, or
 - Cl;

wherein R¹ is

- 25
- CHO,
 - COCH₃,
 - COCHCl₂,
 - COCHF₂,
 - CO₂CH₃,
 - SO₂CH₃, or
 - 30 -COCH₂OH.

CHART III - MORPHOLINES - BRIDGED MORPHOLINES

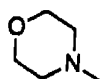
5



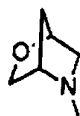
IX

wherein Q² is

10



III-A



III-B

15

wherein X¹ and X² are independently

-H,

-F, or

-Cl;

20 wherein R¹ is

-CHO,

-COCH₃,

-COCHCl₂,

-COCHF₂,

25

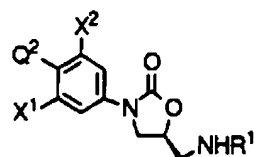
-CO₂CH₃,

-SO₂CH₃, or

-COCH₂OH.

CHART IV - AZETIDINES

5



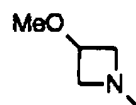
IX

wherein Q^2 is

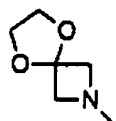
10



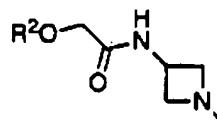
IV-A



IV-I

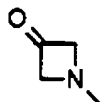


IV-B

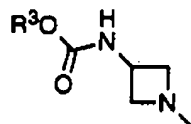


IV-J

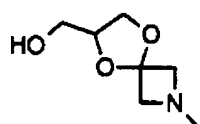
15



IV-C

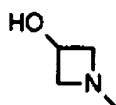


IV-K

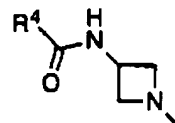


IV-D

20

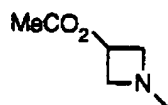


IV-E

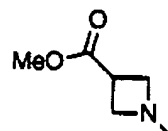


IV-L

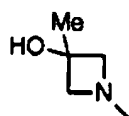
25



IV-F

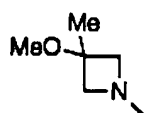


IV-M

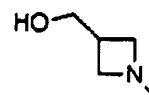


IV-G

30



IV-H



IV-N

CHART IV - AZETIDINES (Continued)

wherein X^1 and X^2 are independently

- 5 -H,
 -F, or
 -Cl;

wherein R^1 is

- CHO,
 -COCH₃,
10 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 -COCH₂OH;

15 wherein R^2 is

- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

20 wherein R^3 is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

25 wherein R^4 is

- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

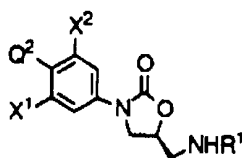
CHART IV- AZETIDINES (Continued)

-CH₂-(aryl), or

-cycloalkyl (rings of 3-6 carbons).

CHART V - PYRROLIDINES

5



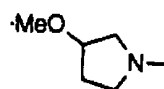
IX

wherein Q² is

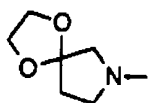
10



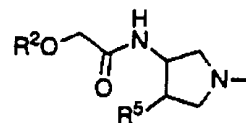
V-A



V-I

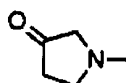


V-B

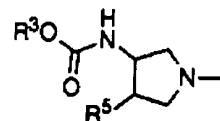


V-J

15

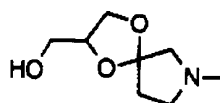


V-C

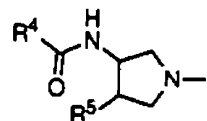


V-K

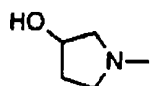
20



V-D

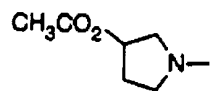


V-L

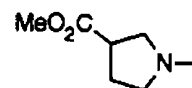


V-E

25

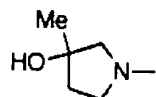


V-F

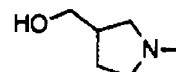


V-M

30

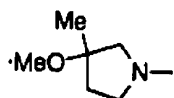


V-G



V-N

35



V-H

CHART V - PYRROLIDINES (Continued)

wherein X^1 and X^2 are independently

- 5 -H,
 -F, or
 -Cl;

wherein R^1 is

- CHO,
 -COCH₃,
10 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 -COCH₂OH;

15 wherein R^2 is

- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

20 wherein R^3 is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

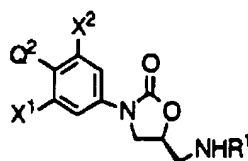
25 wherein R^4 is

- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

CHART V - PYRROLIDINES (Continued)

- CH₂-(aryl), or
-cycloalkyl (rings of 3-6 carbons);
5 wherein R⁵ is
-H,
-CH₃,
-CH₂CH₃, or
-CH₂CH₂CH₃.
10

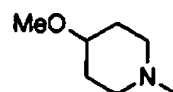
CHART VI - PIPERIDINES



IX

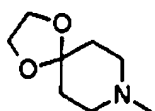
wherein Q^2 is

VI-A

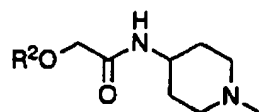


VI-I

10

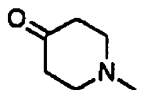


VI-B

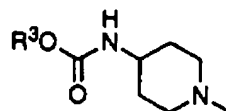


VI-J

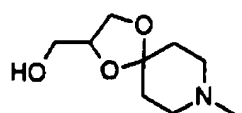
15



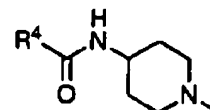
VI-C



VI-K

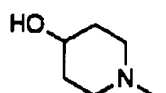


VI-D

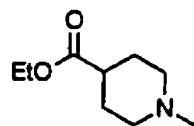


VI-L

20

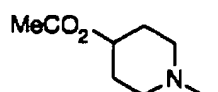


VI-E

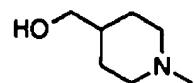


VI-M

25

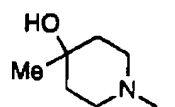


VI-F

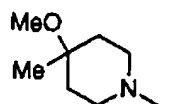


VI-N

30



VI-G



VI-H

35

CHART VI - PIPERIDINES (Continued)

wherein X^1 and X^2 are independently

-H,

5 -F, or

-Cl;

wherein R^1 is

-CHO,

-COCH₃,

10 -COCHCl₂,

-COCHF₂,

-CO₂CH₃,

-SO₂CH₃, or

COCH₂OH;

15 wherein R^2 is

-H,

-CH₃,

-CH₂Ph, or

-COCH₃;

20 wherein R^3 is

-CH₃,

-CH₂CH₃,

-CH₂CH₂CH₃, or

-phenyl;

25 wherein R^4 is

-H,

-CH₃,

-CH₂CH₃,

-CH₂CH₂CH₃,

30 -CH₂CH₂CH₂CH₃,

-phenyl,

-CH₂Cl,

-CHCl₂,

CH₂F,

35 -CHF₂,

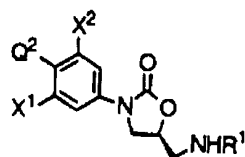
-substituted aryl,

CHART VI - PIPERIDINES (continued)

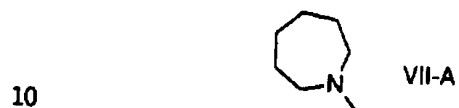
-CH₂-(aryl), or

-cycloalkyl (rings of 3-6 carbons).

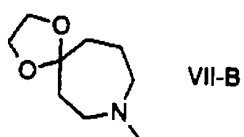
CHART VII - AZEPINES



IX

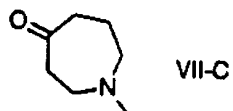
wherein Q^2 is

10

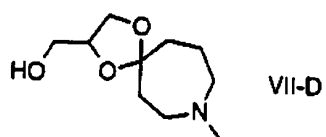


VII-B

15

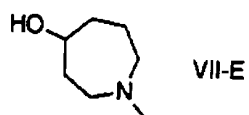


VII-C



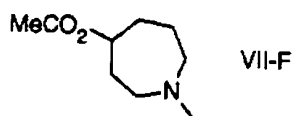
VII-D

20



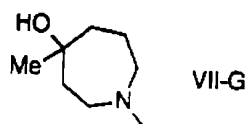
VII-E

25

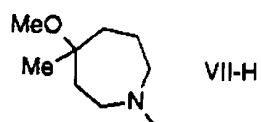


VII-F

30

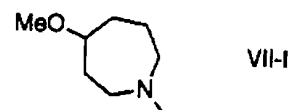


VII-G

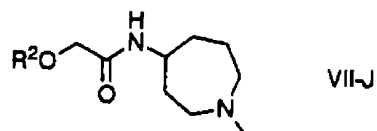


VII-H

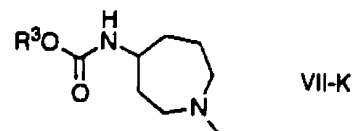
35



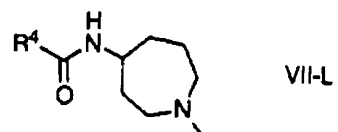
VII-I



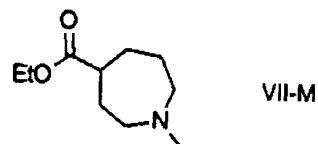
VII-J



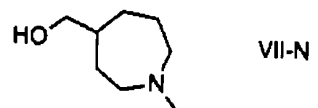
VII-K



VII-L



VII-M



VII-N

CHART VII - AZEPINES (Continued)

wherein X^1 and X^2 are independently

- 5 -H,
 -F, or
 -Cl;

wherein R^1 is

- CHO,
 -COCH₃,
10 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 -COCH₂OH;

15 wherein R^2 is

- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

20 wherein R^3 is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

25 wherein R^4 is

- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

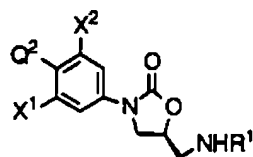
CHART VII - AZEPINES (Continued)

-CH₂-(aryl), or

-cycloalkyl (rings of 3-6 carbons).

CHART VIII - PIPERAZINES

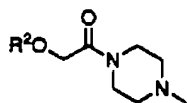
5



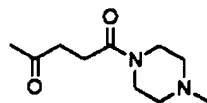
IX

wherein Q² is

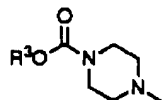
10



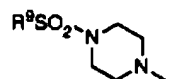
VIII-A



VIII-F

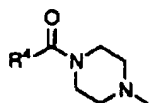


VIII-B

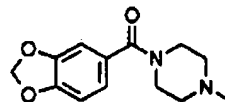


VIII-G

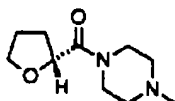
15



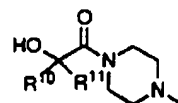
VIII-C



VIII-H

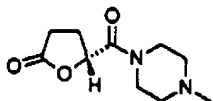


VIII-D

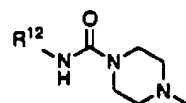


VIII-I

20



VIII-E



VIII-J

25 wherein X¹ and X² are independently

-H,
-F, or
-Cl;

wherein R¹ is

30

-CHO,
-COCH₃,
-COCHCl₂,
-COCHF₂,
-CO₂CH₃,

35

-SO₂CH₃, or
-COCH₂OH;

CHART VIII - PIPERAZINES (Continued)

wherein R^2 is

- 5 -H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

wherein R^3 is

- 10 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

wherein R^4 is

- 15 -H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
 -CH₂CH₂CH₂CH₃,
 -phenyl,
20 -CH₂Cl,
 -CHCl₂,
 CH₂F,
 -CHF₂,
 -substituted aryl,
25 -CH₂-(aryl), or
 -cycloalkyl (rings of 3-6 carbons);

wherein R^9 is

- CH₃,
 -CH₂Cl,
30 -CH₂CH=CH₂,
 substituted aryl, or
 -CH₂CN;

wherein R^{10} and R^{11} are independently

- H,
35 -CH₃, or
 -together form a cyclopropyl ring;

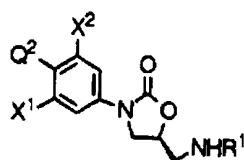
CHART VIII - PIPERAZINES (Continued)

wherein R¹² is

- 5 -CH₂Ph, or
 -substituted aryl.

CHART IX - PYRROLOPYRROLIDINES

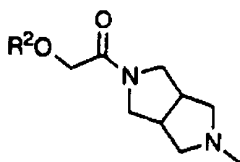
5



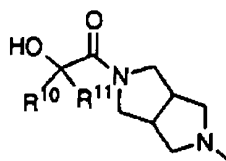
IX

wherein Q² is

10

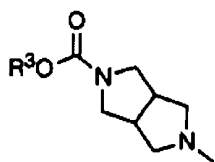


IX-A

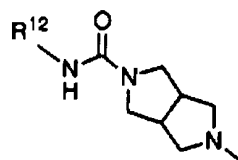


IX-E

15

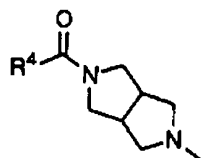


IX-B



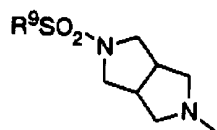
IX-F

20



IX-C

25



IX-D

wherein X¹ and X² are independently

30

-H,

-F, or

-Cl;

CHART IX - PYRROLOPYRROLIDINES (Continued)

wherein R¹ is

- 5 -CHO,
 -COCH₃,
 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
10 -COCH₂OH;

wherein R² is

- H,
 -CH₃,
 -CH₂Ph, or
15 -COCH₃;

wherein R³ is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
20 -phenyl;

wherein R⁴ is

- H,
 -CH₃,
 -CH₂CH₃,
25 -CH₂CH₂CH₃,
 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
30 -CH₂F,
 -CHF₂,
 -substituted aryl,
 -CH₂-(aryl), or
 -cycloalkyl (rings of 3-6 carbons);

35 wherein R⁹ is

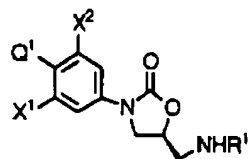
- CH₃,

CHART IX - PYRROLOPYRROLIDINES (Continued)

- 5 -CH₂Cl,
 -CH₂CH=CH₂,
 substituted aryl, or
 -CH₂CN;
 wherein R¹⁰ and R¹¹ are independently
 -H,
 -CH₃, or
10 -together form a cyclopropyl ring;
 wherein R¹² is
 -CH₂Ph, or
 -substituted aryl.

CHART X - THIAZOLIDINES

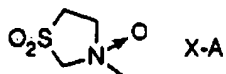
5



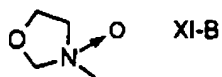
I

wherein Q¹ is

10



X-A



XI-B

15

wherein X¹ and X² are independently

-H,

-F, or

-Cl;

20 wherein R¹ is

-CHO,

-COCH₃,

-COCHCl₂,

-COCHF₂,

25

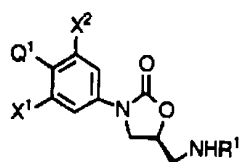
-CO₂CH₃,

-SO₂CH₃, or

-COCH₂OH.

CHART XI - THIOMORPHOLINES - BRIDGED THIOMORPHOLINES

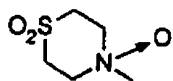
5



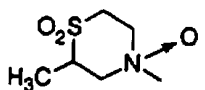
I

wherein Q¹ is

10

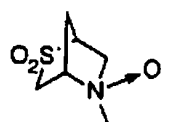


XI-A



XI-B

15



XI-C

wherein X¹ and X² are independently

20

-H,

-F, or

-Cl;

wherein R¹ is

-CHO,

25

-COCH₃,

-COCHCl₂,

-COCHF₂,

-CO₂CH₃,

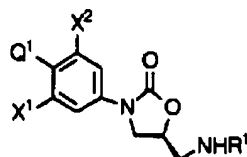
-SO₂CH₃, or

30

-COCH₂OH.

CHART XII - MORPHOLINES - BRIDGED MORPHOLINES

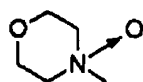
5



I

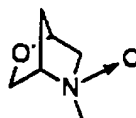
wherein Q¹ is

10



XII-A

15



XII-B

wherein X¹ and X² are independently

-H,

-F, or

20

-Cl;

wherein R¹ is

-CHO,

-COCH₃,

-COCHCl₂,

25

-COCHF₂,

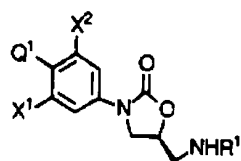
-CO₂CH₃,

-SO₂CH₃, or

-COCH₂OH.

CHART XIII - AZETIDINES

5



I

wherein Q^1 is

10

15

20

25

30

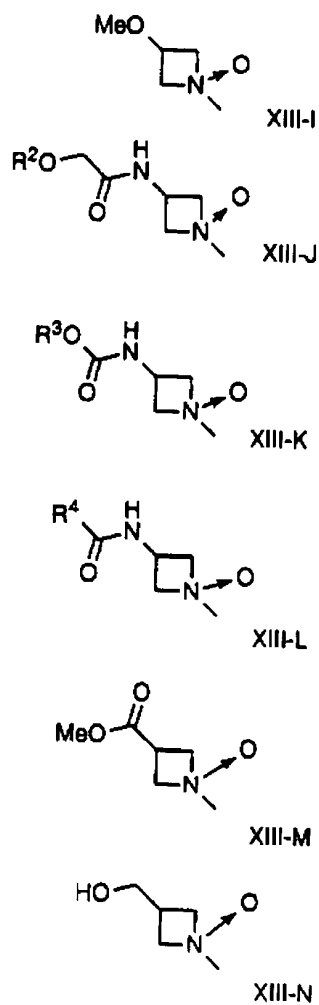
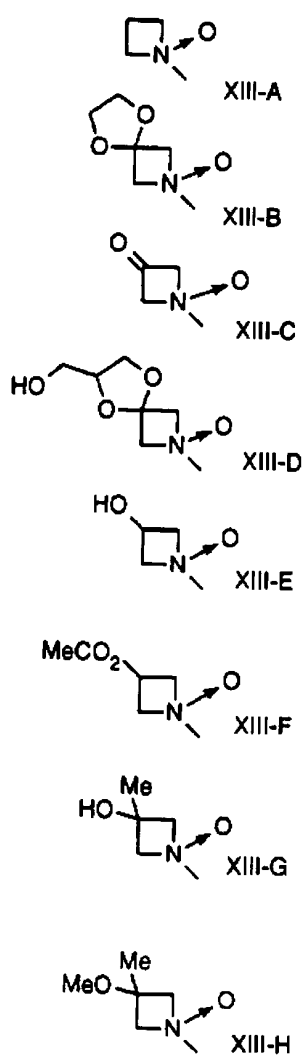


CHART XIII - AZETIDINES (Continued)

wherein X^1 and X^2 are independently

- H,
5 -F, or
 -Cl;

wherein R^1 is

- CHO,
 -COCH₃,
10 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 -COCH₂OH;

15 wherein R^2 is

- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

20 wherein R^3 is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

25 wherein R^4 is

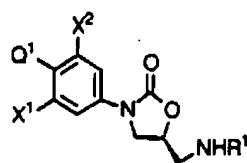
- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

CHART XIII- AZETIDINES (Continued)

-CH₂-(aryl), or
-cycloalkyl (rings of 3-6 carbons).

CHART XIV - PYRROLIDINES

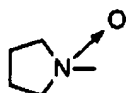
5



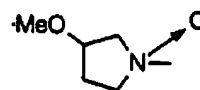
I

wherein Q^1 is

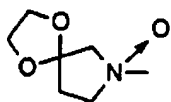
10



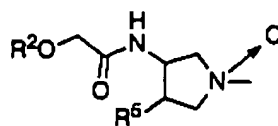
XIV-A



XIV-I

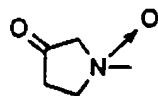


XIV-B

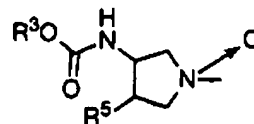


XIV-J

15

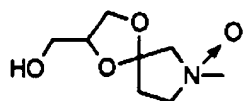


XIV-C

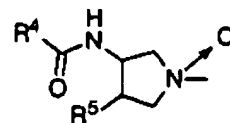


XIV-K

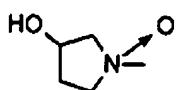
20



XIV-D

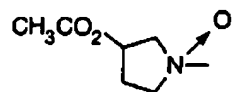


XIV-L

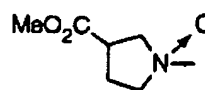


XIV-E

25

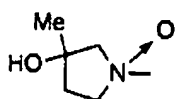


XIV-F

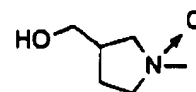


XIV-M

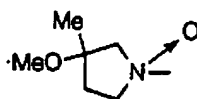
30



XIV-G



XIV-N



XIV-H

35

CHART XIV - PYRROLIDINES (Continued)

wherein X^1 and X^2 are independently

- 5 -H,
 -F, or
 -Cl;

wherein R^1 is

- CHO,
 -COCH₃,
10 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 -COCH₂OH;

15 wherein R^2 is

- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

20 wherein R^3 is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

25 wherein R^4 is

- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

CHART XIV - PYRROLIDINES (Continued)

-CH₂-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

5 wherein R⁵ is

-H,

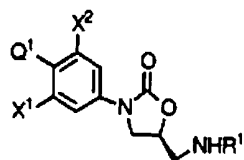
-CH₃,

-CH₂CH₃, or

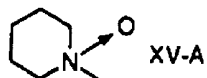
-CH₂CH₂CH₃.

10

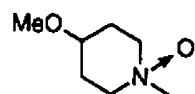
CHART XV - PIPERIDINES



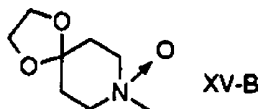
I

wherein Q¹ is

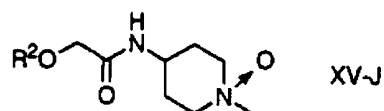
XV-A



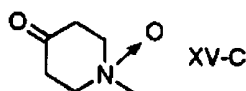
XV-I



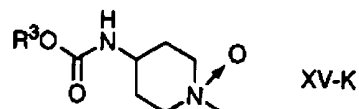
XV-B



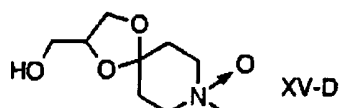
XV-J



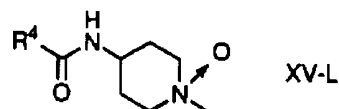
XV-C



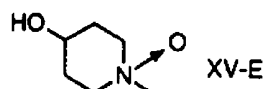
XV-K



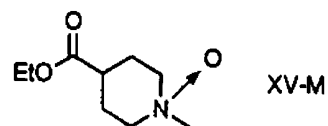
XV-D



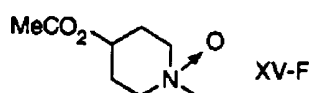
XV-L



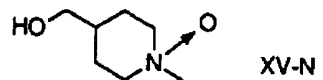
XV-E



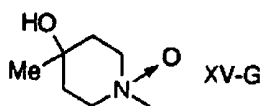
XV-M



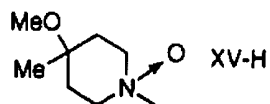
XV-F



XV-N



XV-G



XV-H

CHART XV - PIPERIDINES (Continued)

wherein X^1 and X^2 are independently

- 5 -H,
 -F, or
 -Cl;

wherein R^1 is

- CHO,
 -COCH₃,
10 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 COCH₂OH;

15 wherein R^2 is

- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

20 wherein R^3 is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

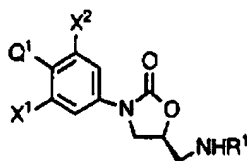
25 wherein R^4 is

- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

CHART XV - PIPERIDINES (continued)

-CH₂-(aryl), or
-cycloalkyl (rings of 3-6 carbons).

CHART XVI - AZEPINES



I

wherein Q¹ is

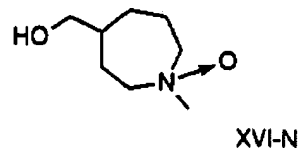
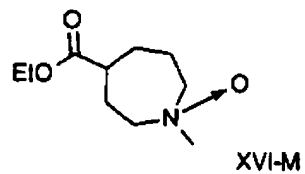
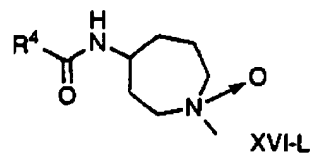
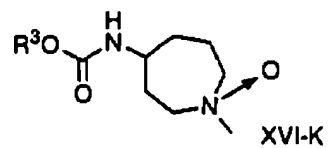
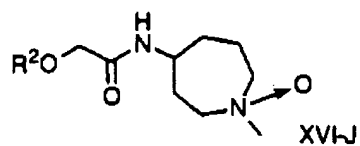
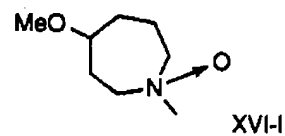
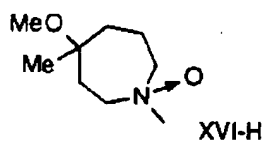
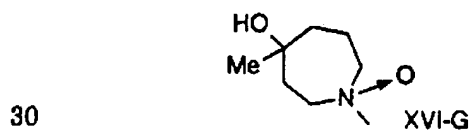
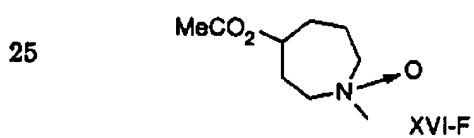
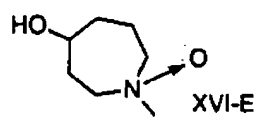
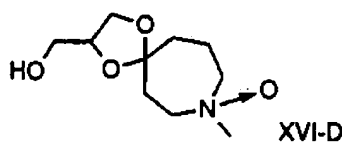
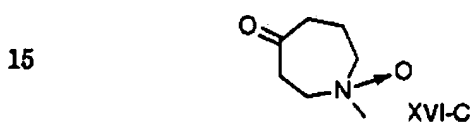
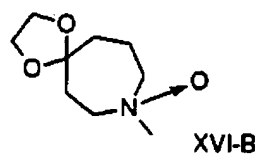
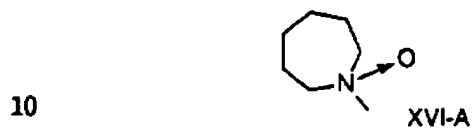


CHART XVI - AZEPINES (Continued)

wherein X^1 and X^2 are independently

- H,
5 -F, or
 -Cl;

wherein R^1 is

- CHO,
 -COCH₃,
10 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 -COCH₂OH;

15 wherein R^2 is

- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;

20 wherein R^3 is

- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;

25 wherein R^4 is

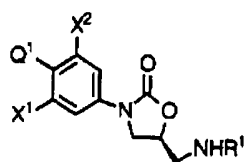
- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

CHART XVI - AZEPINES (Continued)

-CH₂-(aryl), or
-cycloalkyl (rings of 3-6 carbons).

CHART XVII - PIPERAZINES

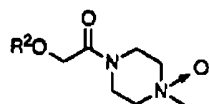
5



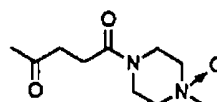
I

wherein Q¹ is

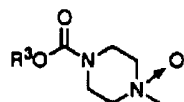
10



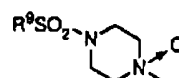
XVII-A



XVII-F

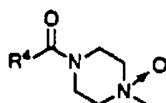


XVII-B

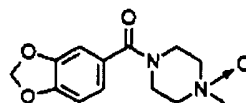


XVII-G

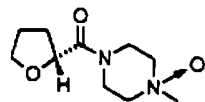
15



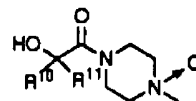
XVII-C



XVII-H

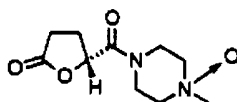


XVII-D

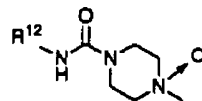


XVII-I

20



XVII-E



XVII-J

25

30

35

CHART XVII - PIPERAZINES (Continued)

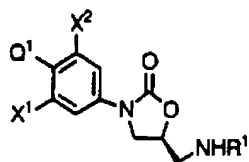
- wherein X^1 and X^2 are independently
- 5 -H,
 -F, or
 -Cl;
- wherein R^1 is
- 10 -CHO,
 -COCH₃,
 -COCHCl₂,
 -COCHF₂,
 -CO₂CH₃,
 -SO₂CH₃, or
 -COCH₂OH;
- 15 wherein R^2 is
- H,
 -CH₃,
 -CH₂Ph, or
 -COCH₃;
- 20 wherein R^3 is
- CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃, or
 -phenyl;
- 25 wherein R^4 is
- H,
 -CH₃,
 -CH₂CH₃,
 -CH₂CH₂CH₃,
30 -CH₂CH₂CH₂CH₃,
 -phenyl,
 -CH₂Cl,
 -CHCl₂,
 CH₂F,
35 -CHF₂,
 -substituted aryl,

CHART XVII - PIPERAZINES (Continued)

- CH₂-(aryl), or
-cycloalkyl (rings of 3-6 carbons);
- 5 wherein R⁹ is
-CH₃,
-CH₂Cl,
-CH₂CH=CH₂,
substituted aryl, or
- 10 -CH₂CN;
wherein R¹⁰ and R¹¹ are independently
-H,
-CH₃, or
-together form a cyclopropyl ring;
- 15 wherein R¹² is
-CH₂Ph, or
-substituted aryl.

CHART XVIII - PYRROLOPYRROLIDINES

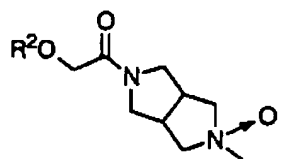
5



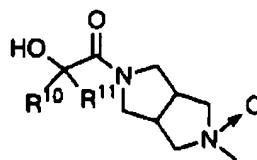
I

wherein Q¹ is

10

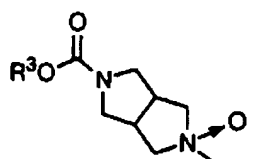


XVIII-A

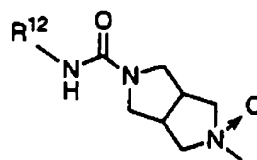


XVIII-E

15

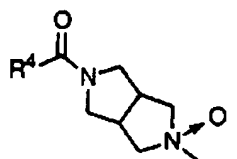


XVIII-B



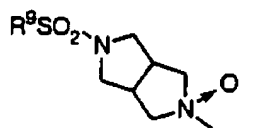
XVIII-F

20



XVIII-C

25



XVIII-D

30 wherein X¹ and X² are independently

-H,

-F, or

-Cl;

CHART XVIII - PYRROLOPYRROLIDINES (Continued)

wherein R¹ is

- CHO,
- 5 -COCH₃,
- COCHCl₂,
- COCHF₂,
- CO₂CH₃,
- SO₂CH₃, or
- 10 - COCH₂OH;

wherein R² is

- H,
- CH₃,
- CH₂Ph, or
- 15 -COCH₃;

wherein R³ is

- CH₃,
- CH₂CH₃,
- CH₂CH₂CH₃, or
- 20 -phenyl;

wherein R⁴ is

- H,
- CH₃,
- CH₂CH₃,
- 25 -CH₂CH₂CH₃,
- CH₂CH₂CH₂CH₃,
- phenyl,
- CH₂Cl,
- CHCl₂,
- 30 -CH₂F,
- CHF₂,
- substituted aryl,
- CH₂-(aryl), or
- cycloalkyl (rings of 3-6 carbons);

35 wherein R⁹ is

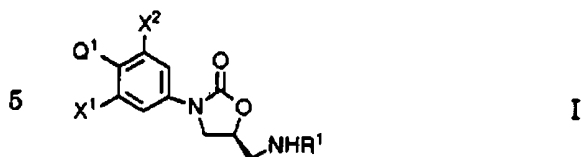
- CH₃,

CHART XVIII - PYRROLOPYRROLIDINES (Continued)

- 5 -CH₂Cl,
 -CH₂CH=CH₂,
 substituted aryl, or
 -CH₂CN;
 wherein R¹⁰ and R¹¹ are independently
 -H,
 -CH₃, or
10 -together form a cyclopropyl ring;
 wherein R¹² is
 -CH₂Ph, or
 -substituted aryl.

CLAIMS

1. A compound of the formula I



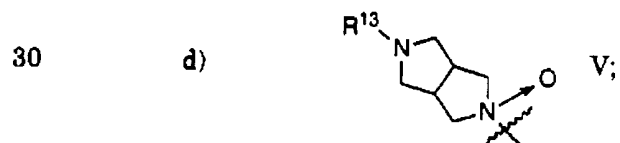
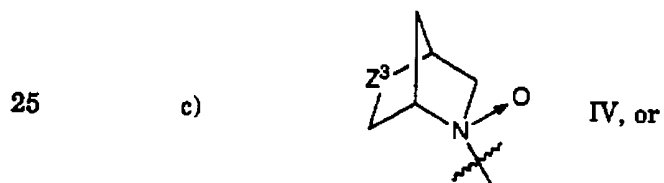
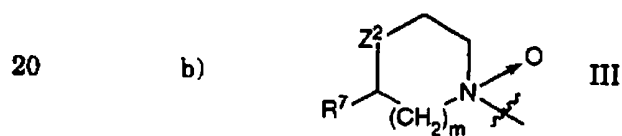
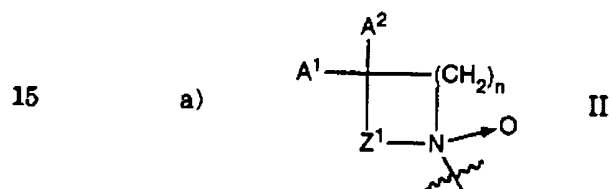
wherein X^1 and X^2 are independently

-H,

10 -F, or

-Cl;

wherein Q^1 is:



wherein Z^1 is

a) $-CH_2-$, or

35 b) $-CH(R^5)-CH_2-$;

wherein Z^2 is

- a) $-\text{O}_2\text{S}-$,
- b) $-\text{O}-$, or
- c) $-\text{N}(\text{R}^8)-$;

wherein Z^3 is

- 5 a) $-\text{O}_2\text{S}-$, or
- b) $-\text{O}-$;

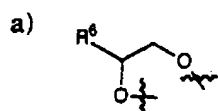
wherein A^1 is

- a) $\text{H}-$, or
- b) CH_3- ;

10 wherein A^2 is

- a) $\text{H}-$,
- b) $\text{HO}-$,
- c) CH_3CO_2- ,
- d) CH_3- ,
- 15 e) $\text{CH}_3\text{O}-$,
- f) $\text{R}^2\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$
- g) $\text{R}^3\text{O}-\text{C}(\text{O})-\text{NH}-$,
- h) $\text{R}^4-\text{C}(\text{O})-\text{NH}-$,
- i) $(\text{C}_1-\text{C}_2)\text{alkyl}-\text{O}-\text{C}(\text{O})-$, or
- 20 j) $\text{HO}-\text{CH}_2-$; or

A^1 and A^2 taken together are:



or

25

- b) $\text{O}=\text{C}-$

;

wherein R^1 is

- a) $-\text{CHO}$,
- 30 b) $-\text{COCH}_3$,
- c) $-\text{COCHCl}_2$,
- d) $-\text{COCHF}_2$,
- e) $-\text{CO}_2\text{CH}_3$,
- f) $-\text{SO}_2\text{CH}_3$, or
- 35 g) $-\text{COCH}_2\text{OH}$;

wherein R^2 is

- a) H-,
- b) CH₃-,
- c) phenyl-CH₂-, or
- d) CH₃C(O)-;

5 wherein R³ is

- a) (C₁-C₃)alkyl-, or
- b) phenyl-;

wherein R⁴ is

- a) H-,
- 10 b) (C₁-C₄)alkyl,
- c) aryl -(CH₂)_p,
- d) ClH₂C-,
- e) Cl₂HC-,
- f) FH₂C-,
- 15 g) F₂HC-, or
- h) (C₃-C₆)cycloalkyl;

wherein R⁵ is

- a) H-, or
- b) (C₁-C₃)alkyl;

20 wherein R⁶ is

- a) H-, or
- b) HOH₂C-;

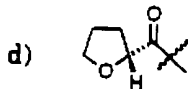
wherein R⁷ is

- a) H-, or
- 25 b) H₃C-;

wherein R⁸ is

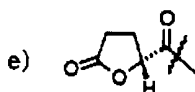
- a) R²O-C(R₁₀)(R₁₁)-C(O)-,
- b) R³O-C(O)-,
- c) R⁴-C(O)-,

30



VI ,

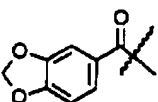
35



VII ,

f) $\text{H}_3\text{C}-\text{C}(\text{O})-(\text{CH}_2)_2-\text{C}(\text{O})-$,

g) R^9-SO_2- ,

h)  VIII, or

5

i) $\text{R}^{12}-\text{NH}-\text{C}(\text{O})-$;

wherein R^9 is

a) $-\text{CH}_3$,

10 b) $-\text{CH}_2\text{Cl}$

c) $-\text{CH}_2\text{CH}=\text{CH}_2$,

d) aryl, or

e) $-\text{CH}_2\text{CN}$;

wherein R^{10} and R^{11} are independently

15 a) $\text{H}-$,

b) CH_3- ; or

R^{10} and R^{11} taken together are $-\text{CH}_2-\text{CH}_2-$;

wherein R^{12} is $-(\text{CH}_2)_p$ -aryl;

wherein R^{13} is

20 a) $\text{R}^2\text{O}-\text{C}(\text{R}_{10})(\text{R}_{11})-\text{C}(\text{O})-$,

b) $\text{R}^3\text{O}-\text{C}(\text{O})-$,

c) $\text{R}^4-\text{C}(\text{O})-$,

d) R^9-SO_2- , or

e) $\text{R}^{12}-\text{NH}-\text{C}(\text{O})-$;

25 wherein m is zero (0) or one (1);

wherein n is one (1) to three (3), inclusive;

wherein p is zero (0) or one (1);

wherein aryl is phenyl substituted with zero (0) or one (1) of the following:

a) $-\text{F}$,

30 b) $-\text{Cl}$,

c) $-\text{OCH}_3$,

d) $-\text{OH}$,

e) $-\text{NH}_2$,

f) $-(\text{C}_1-\text{C}_4)\text{alkyl}$,

35 g) $-\text{O}-\text{C}(\text{O})-\text{OCH}_3$,

h) $-\text{NO}_2$, or

i) -CN;

with the following provisos:

- 1) in the moiety of formula II, Z^1 is $-\text{CH}(\text{R}^5)-\text{CH}_2-$ wherein R^5 is $(\text{C}_1-\text{C}_3)\text{alkyl}$, only when n is one (1), A^1 is H and A^2 is $\text{R}^2\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$, $\text{R}^3\text{O}-\text{C}(\text{O})-\text{NH}-$, or $\text{R}^4-\text{C}(\text{O})-\text{NH}-$; and
 - 2) in the moiety of formula II, when Z^1 is $-\text{CH}_2-$, n is one (1).
2. The compound of claim 1 wherein Q^1 is the moiety of formula II.
 3. The compound of claim 1 wherein Q^1 is the moiety of formula III.
 4. The compound of claim 1 wherein Q^1 is the moiety of formula IV.
 5. The compound of claim 1 wherein Q^1 is the moiety of formula V.
 6. The compound of claim 1 wherein one of X^1 and X^2 is -H and the other is -F or wherein X^1 is -F and X^2 is -F.
 7. The compound of claim 1 wherein R^1 is acetyl.
 8. The compound of claim 1 selected from the group consisting of:
 - (S)-N-[[3-[3-fluoro-4-(1,1-dioxothiazolidin-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
 - (S)-N-[[3-[3-fluoro-4-(3-oxazolidinyl)]phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide N-oxide;
 - (S)-N-[[3-[3-fluoro-4-(1,1-dioxothiomorpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
 - (S)-N-[[3-[3-fluoro-4-[(1S,4S)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
 - (S)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;
 - (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide N-oxide;
 - (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-hydroxyacetamide N-oxide;
 - (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-

- formamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-
 methylcarbamate N-oxide;
 (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-
 5 dichloroacetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-
 oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidiny]phenyl]-2-oxo-5-oxazolidinyl]-
 methyl]acetamide N-oxide;
 10 (S)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidiny]phenyl]-2-oxo-5-
 oxazolidinyl]methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[3-[(methoxycarbonyl)amino]-1-azetidiny]phenyl]-2-oxo-
 5-oxazolidinyl]methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[3-[(hydroxyacetyl)amino]-1-azetidiny]phenyl]-2-oxo-5-
 15 oxazolidinyl]methyl]acetamide N-oxide;
 (S)-N-[[3-[3-Fluoro-4-(3-hydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]-
 methyl]acetamide N-oxide;
 (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(hydroxyacetyl)amino)-4-methylpyrrolidinyl]-
 phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
 20 (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)-
 phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;
 (S)-N-[3-[4-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-
 oxazolidin-5-ylmethyl]-acetamide N-oxide;
 (S)-N-[3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-
 25 phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;
 (S)-1-[4-[5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-
 piperidine-4-carboxylic acid ethyl ester N-oxide;
 (S)-N-[3-[3-fluoro-4-(4-hydroxymethylpiperidin-1-yl)-phenyl]-2-oxo-
 oxazolidin-5-ylmethyl]-acetamide N-oxide;
 30 (S)-N-[3-[3-fluoro-4-(4-oxoazepin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-
 acetamide N-oxide;
 (S)-4-[4-[5-((acetyl)amino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-1-
 piperazinecarboxylic acid, methyl ester N-oxide;
 (S)-4-[4-[5-((acetyl)amino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-
 35 piperazinecarboxylic acid, ethyl ester N-oxide;
 (S)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-

- yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[*cis*-3-[(cyclopropyl)carbonyl]-3,7-diazabicyclo[3.3.0]-
 octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[*cis*-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.0]octan-7-
 5 yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide N-oxide;
 (S)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-
 oxazolidinyl)methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-
 5-oxazolidinyl)methyl]acetamide N-oxide;
 10 (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-
 piperazinecarboxylic acid, methyl ester N-oxide; and
 (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-
 1-piperazinecarboxylic acid, methyl ester N-oxide.
- 15 9. The compound of claim 8 selected from the group consisting of:
 (S)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl)methyl]
 acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]-
 acetamide N-oxide;
 20 (S)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-
 oxazolidinyl)methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-
 oxazolidinyl)methyl]acetamide N-oxide;
 (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-
 25 1-piperazinecarboxylic acid, methyl ester N-oxide; and
 (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-
 1-piperazinecarboxylic acid, methyl ester N-oxide.
10. The compound of claim 1 selected from the group consisting of:
 30 (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-
 oxazolidinyl]-methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-
 oxazolidinyl)methyl]acetamide N-oxide;
 (S)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-
 35 oxazolidinyl]-methyl]acetamide N-oxide;
 (S)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-

oxazolidinyl]-methyl]acetamide N-oxide;

(S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide; and

(S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

INTERNATIONAL SEARCH REPORT

International Application No.
PC1/US 96/14135

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D263/20 A61K31/42 C07D417/10 C07D495/08 C07D491/08
C07D413/10 C07D471/04 C07D491/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 cited in the application see claims ---	1-10
Y	WO 93 23384 A (THE UPJOHN COMPANY) 25 November 1993 cited in the application see claims ---	1-10
Y	WO 92 18469 A (BRITISH TECHNOLOGY GROUP LTD) 29 October 1992 cited in the application see page 2, lines 8-21 and page 12, lines 16-31 see claims --- -/--	1-7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

9 December 1996

Date of mailing of the international search report

17.12.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/14135

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y.	US 4 722 928 A (GEORGE A.BOSWELL ET AL) 2 February 1988 cited in the application see the whole document ---	1-7
Y	WO 95 14684 A (THE UPJOHN COMPANY) 1 June 1995 cited in the application see claims ---	1-10
P,Y	WO 96 15130 A (THE UPJOHN COMPANY) 23 May 1996 cited in the application see claims ---	1-10
P,Y	WO 96 23788 A (PHARMACIA + UPJOHN COMPANY) 8 August 1996 cited in the application see claims ---	1-10
P,Y	WO 96 13502 A (THE UPJOHN COMPANY) 9 May 1996 cited in the application see claims ---	1-10
P,Y	WO 95 25106 A (THE UPJOHN COMPANY) 21 September 1995 cited in the application see claims ---	1-10
E	WO 96 35691 A (PHARMACIA + UPJOHN COMPANY) 14 November 1996 see claims -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/US 96/14135

PC/US 96/14135

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9507271	16-03-95	AU-A- 7557094	27-03-95
		CA-A- 2168560	16-03-95
		CN-A- 1130379	04-09-96
		EP-A- 0717738	26-06-96

WO-A-9323384	25-11-93	AU-B- 668733	16-05-96
		AU-A- 4287793	13-12-93
		CN-A- 1079964	29-12-93
		CZ-A- 9402505	16-08-95
		EP-A- 0640077	01-03-95
		FI-A- 945246	08-11-94
		HU-A- 72296	29-04-96
		HU-A- 9500659	28-11-95
		JP-T- 7506829	27-07-95
		NO-A- 944237	04-01-95
		SK-A- 133794	07-06-95
		US-A- 5547950	20-08-96
		ZA-A- 9302855	24-10-94

WO-A-9218469	29-10-92	AT-T- 132136	15-01-96
		AU-B- 660883	06-07-95
		AU-A- 1537692	17-11-92
		CA-A- 2108256	13-10-92
		DE-D- 69207182	08-02-96
		DE-T- 69207182	15-05-96
		EP-A- 0579646	26-01-94
		ES-T- 2082461	16-03-96
		GB-A, B 2254613	14-10-92
		JP-T- 6506923	04-08-94
		US-A- 5461078	24-10-95
		ZA-A- 9202641	11-10-93

US-A-4722928	02-02-88	JP-A- 6024988	01-02-94
		JP-B- 7047538	24-05-95
		JP-A- 6048944	22-02-94
		JP-B- 7121946	25-12-95
		JP-B- 6099435	07-12-94
		JP-A- 62138429	22-06-87
		US-A- 4990617	05-02-91

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/US 96/14135

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9514684	01-06-95	AU-A- 8010394	13-06-95
		CA-A- 2174107	01-06-95
		EP-A- 0730591	11-09-96
		ZA-A- 9407885	09-04-96
WO-A-9615130	23-05-96	AU-A- 3889095	06-06-96
WO-A-9623788	08-08-96	AU-A- 4899896	21-08-96
WO-A-9613502	09-05-96	AU-A- 3625495	23-05-96
WO-A-9525106	21-09-95	JP-A- 8073455	19-03-96
		AU-A- 2099995	03-10-95
		CA-A- 2183972	21-09-95
WO-A-9635691	14-11-96	NONE	

THIS PAGE BLANK (USPT)